

Nicotine as an Addictive Substance: A Critical Examination of the Basic Concepts and Empirical Evidence

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The present review is a critical analysis of the concepts behind and the empirical data supporting the view that tobacco use represents an addiction to nicotine. It deals with general aspects of the notion of addiction, while concentrating on specific problems associated with incorporating nicotine into current frameworks. The notion of addiction suffers from unprecedented definitional difficulties. The definitions offered by various authorities are very different, even contradictory. Definitions that reasonably include nicotine are so broad and vague that they allow many trivial things, such as salt, sugar, and watching television, to be considered addictive. Definitions that exclude the trivia also exclude nicotine. The addiction hypothesis, in general, is strongly shaped by views that certain drugs bring about a molecular level subversion of rationality. The main human evidence for this is verbal reports of smokers who say that they can't quit. On the other hand, the existence of many millions of successful quitters suggests that most people can quit. Some smokers don't quit, but whether they can't is another matter. The addiction hypothesis would be greatly strengthened by the demonstration that any drug of abuse produces special changes in the brain. It has yet to be shown that any drug produces changes in the brain different from those produced by many innocuous substances and events. The effects of nicotine on the brain are similar to those of sugar, salt, exercise, and other harmless substances and events. Apart from numerous conceptual and definitional inadequacies with the addiction concept in general, the notion that nicotine is addictive lacks reasonable empirical support. Nicotine does not have the properties of reference drugs of abuse. There are so many findings that conflict so starkly with the view that nicotine is addictive that it increasingly appears that adhering to the nicotine addiction thesis is only defensible on extra-scientific grounds.

Introduction

The addiction model has dominated smoking research for over a generation (Benowitz, 1988; Benowitz, 1996; Henningfield & Heishman, 1995; Peele, 1990a; Rose, 1996; Russell, 1990a; Stolerman & Jarvis, 1995). Tobacco smoke is said to contain numerous agents that cause ill health (Gupta, Murti, & Bhonsle, 1996; Trichopoulos, Li, & Hunter 1996) as well as a powerful addictive drug, nicotine (Altman et al., 1996; Anonymous, 1996; Benowitz, 1996; Busto, Bendayan, & Sellers, 1989; Dewey et al., 1999; Griffiths, 1996; Grunberg, 1994; Henningfield, 1984; Henningfield, Cohen, & Slade, 1991; Rose, 1996; Shytle, Silver, & Sanberg, 1996; Stephenson, 1996; Waldum, Nilsen, Nilsen, Rorvik, Syversen, Sandvik, Haugen, Torp, & Brenna, 1996; Altman et al., 1996). According to the dominant model, as the nicotine addiction develops, the smoker becomes progressively less able to stop (Anonymous, 1995; Foulds & Ghodse, 1995; Frantzen, 1996; Henningfield, 1983). The essence of the nicotine addiction hypothesis is that smokers are unable to stop because nicotine changes the brain in such a way as to perpetuate its use. More broadly, drug addictions are seen as representing brain dysfunctions. It is this hypothesis and related issues that are examined in the present work.

The 1988 Surgeon General's Report on Smoking and Health states the nicotine addiction viewpoint succinctly:

Cigarettes and other forms of tobacco are addicting. Nicotine is the drug in tobacco that

causes addiction. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine. (United States Department of Health and Human Services, 1988, p. 4)

The addiction model continues to generate strong views. This is reflected in titles such as: "The nicotine addiction trap: A 40-year sentence for four cigarettes" (Russell, 1990b, p. 293). Goldstein refers to smoking as "addictive suicide" (Goldstein, 1994, p. 7). Another article indicted cigarettes as being among the most addictive substances known to man (Schelling, 1992). The eminent biologist, D.S. Jordan, who was the first president of Stanford University, expressed his opinion of smoking in 1913: "The boy who smokes cigarettes need not be anxious about his future, he has none" (Sullum, 1996, p. 32).

Thomas Edison stated that cigarette smoke "...has a violent action on the nerve centers, producing degeneration of the cells of the brain, which is quite rapid among boys. Unlike most narcotics this degeneration is permanent and uncontrollable" (Sullum, 1998, p. 32). Edison's statement is a forerunner of the contemporary view that cigarette smoking is maintained by changes in the brain produced by nicotine.

At the moment, it is nearly impossible to find a contemporary document on smoking that doesn't mention nicotine addiction as an incontestable point in the first paragraph. Many believe that the recent admissions of tobacco companies constitute further proof that nicotine is addictive (Allis, Lafferty, McAllister, & van Voorst, 1997; Carey, France, Dunham, & Greising, 1997). This belief is peculiar since the earlier denials of the tobacco companies were widely held to be false and self-serving (Sullum, 1998). The validity of the nicotine addiction hypothesis is not about admissions, assertions, or concessions; it is about logic and data.

Conceptual Analysis of the Addiction Model

With sufficient use, certain drugs are said to change the brain in such a way as to make cessation difficult or impossible (Leshner, 1997, 1998, 1999a, 1999b). Drug users frequently state that they cannot help themselves (Luik, 1996; Schaler, 2000). The nature of this alleged helplessness remains unclear. Drugs such as opiates and cocaine are clearly very enjoyable, and users often report that such drugs produce intense feelings of pleasure (Epstein, Silverman, Henningfield, & Preston 1999; Heishman, Schuh, Schuster, Henningfield, & Goldberg, 2000). It is possible that intense pleasure could account for persistent drug use. On the other hand, drugs such as nicotine have only small and variable subjective effects (Duka, Tasker, Russell, & Stephens, 1998; Rusted, Mackee, Williams, & Willner, 1998). Although smoking may be pleasant, the effects are not at all comparable to traditional drugs of abuse. Nicotine's lack of potent subjective effects necessitates some other sort of mechanism to account for persistent use. This other mechanism requires a unique pharmacological property, a pleasure-independent ability to lead the user into repeated use. However, at the moment there is no evidence of any neural mechanisms that could mediate such an unprecedented effect.

The most direct form of evidence supporting the belief that drugs induce a form of helplessness in certain users is the verbal reports of the users themselves (Davies, 1998; Gori, 1996). That users may not stop is obvious; whether they cannot stop is another matter. The utility of the verbal reports of drug users is compromised by at least two major factors. Drug users, including smokers, tend to suffer from diverse forms of psychopathology (Bergen & Caporaso, 1999; Coelho et al., 2000; Franken & Hendriks, 2000; Holmen, Barrett-Connor, Holmen, & Bjermer, 2000; Riggs, Mikulich, Whitmore, & Crowley, 1999; Stassen et al., 2000; Tanskanen et al., 2000). Thus, even with the best of intentions, the fidelity of their

verbal reports is uncertain (Davies, 1998). However, drug users often do not have good intentions. They tend to explain their behavior in a manner that minimizes personal responsibility (Davies, 1997, 1998; Schaler, 2000). This has clear social and legal advantages. Such considerations suggest that the verbal reports of drug users may not be valid explanations of their behavior (Davies; Schaler). Such reports are, at best, pre-scientific data.

Determining why people continue drug use is greatly complicated by the fact that those who are attracted to drugs are constitutionally quite different from those who are not (Crowley, Mikulich, MacDonald, Young, & Zerbe, 1998; Franken & Hendriks, 2000; Healy & Tranter, 1999). These initial differences confound the interpretation of subsequent results. Random allocation of humans to treatment and control groups is not ethically permissible with dangerous drugs. This necessitates investigating drug use in laboratory species that have little psychopathology, and no motives for dissimulation. Further, in marked contrast to humans, laboratory species can be randomly allocated to potentially dangerous treatments. Attractive though it may be, this approach faces the problem that no drug reliably produces compulsive use in any laboratory species. We will see below that even large doses over long periods of time leave laboratory animals quite indifferent to continued use. Much the same applies to humans. Such findings argue against the view that the propensity to produce cessation difficulties is a property of drugs (Ward, Li, Luedtke, & Emmett-Oglesby, 1996).

If addictive potential is a property of certain substances, it should show the temporal, geographic, and inter-individual stability common to all drug properties. For example, cocaine analgesia has been formally recognized since at least 1884 (Haas, 1995; Hirschmuller, 1995), although it was known to the Incas two thousand years earlier (Siegel, 1985). Cocaine analgesia is equally apparent in Peoria and Peru, and it is seen in everyone who is given the drug. It is reasonable to say that local anesthesia is an inherent property of cocaine. Such constancy is not found for the putative addictive property of drugs (Nencini, 1997b; Nencini, 1997a; US Government Office of Technology Assessment, 1994; Whitbread, 1995). Which drugs are considered addictive varies enormously over time and in different locations. For many years tobacco was considered harmless and cannabis extremely dangerous (Das, 1993; Das & Laddu, 1993). The head of a federal drug agency testified in court that when he tried a marijuana cigarette, he was transformed into a bat and flew around the laboratory (Whitbread & Bonnie, 1970).

Cannabis-induced insanity was a successful defense strategy in several homicide trials (Whitbread & Bonnie). Alarmist views of cannabis are now considered quaint, whereas tobacco use is currently portrayed as a deadly addiction. Such position reversals can only be justified by the appearance of dramatic new empirical evidence or theoretical developments. The fact that no momentous new evidence or theoretical developments have appeared suggests that political and legal considerations have taken precedence over scientific considerations (Davies, 1997; Epstein, 1990; Kutchins & Kirk, 1997; Pandina & Huber, 1990; Peele, 1991; Sullum, 1998).

It is becoming increasingly apparent that problem drug use is not simply a pharmacological issue (Coleman, 1976; Jonnes, 1995; Murray, 1991; Schoberberger, Kunze, & Schmeiser-Rieder, 1997; Shiffman, 1991; Shiffman, Paty, Gnys, Kassel, & Elash, 1995). The use of powerful drugs such as opiates and cocaine is subject to major social-environmental modulation (Coleman, 1976; Krause et al., 1993; Peele, 1987, 1990a, 1990b). Even opiates often do not cause problem behavior in humans (Goode, 1999). Social-environmental factors are likely of even greater importance in the use of commoner substances such as tobacco (Fahrenkrug & Gmel, 1996; Perkins, 1995).

The addiction model is counterproductive to the aim of reducing problem drug use. Since its ascendancy

there has been little progress made in the treatment of drug taking (Chiauzzi & Liljegren, 1993; McMurrin, 1994; Smart, 1994). In spite of a plethora of theory, research, and application, the success rate for treating common drug problems is so poor that it is rarely mentioned in scientific reports. In contrast, some 50 million Americans alone have quit smoking (Fiore, Newcomb, & McBride, 1993; Giovino, Henningfield, Tomar, Escobedo, & Slade, 1995; Orleans & Slade, 1993; Taylor, 1984).

The main reason given by smokers for their failure to stop smoking is that they see themselves as addicted (Henrikus, Jeffery, & Lando, 1995; Stewart et al., 1996). Smokers are widely portrayed as victims of rogue molecular processes in their brains (Chiauzzi & Liljegren, 1993; Russell, 1990b; Schelling, 1992). As long as smoking is portrayed as an inexorable addictive process, the success of cessation programs will be limited by a self-fulfilling prophecy (Coleman, 1976; Drew, 1986; Fingarette, 1979; Fingarette, 1981; Fingarette, 1990; Jensen & Coombs, 1994; Schwartz, 1992).

Defining Addiction

Addiction and related terms have such broad and variable usage that they can mean almost anything (Chiauzzi & Liljegren, 1993; Coleman, 1976; Gori, 1996; Linsen, Zitman, & Breteler, 1995; Stepney, 1996; Warburton, 1985). Addiction is used to describe behaviors ranging from injecting heroin and cocaine, to smoking or chewing tobacco, drinking coffee, eating chocolate, shopping, watching television soap operas (Jaffe, 1992), and falling in love (Griffin-Shelley, 1993). There are reports of addiction to water (Kaplan, 1998), cardiac defibrillators (Fricchione, Olson, & Vlay, 1989), carrots (Cerny & Cerny, 1992; Kaplan 1996), hormone replacement therapy (Bewley & Bewley, 1992), and numerous other unusual entities (Glatt & Cook, 1987; Griffin-Shelley, 1993; Hodge, 1992; Robinson, 1997; Solursh, 1989). The clinical literature is replete with examples of people who develop unfortunate, even destructive, relationships with a great many substances, objects, events, and people (American Psychiatric Association, 1994). It is questionable whether these problems are illuminated by invoking the concept of addiction.

The disarray in this area is reflected in the terminology (Di Chiara, 1995). Reviews often include glossaries explaining just what *they* mean by each of the many terms in common usage in this work (Di Chiara, 1995; Robinson & Berridge, 1993; Stolerman, 1992). This greatly complicates any overall evaluation since different papers often appear to be discussing quite different processes.

Even with respect to drug addiction, there is a great deal of confusion. A recent review identified 126 definitions in 51 different publications (Linsen, Zitman, & Breteler, 1995). And this was only for benzodiazepine addiction. There is no consensus concerning the definition of addiction or the related concepts of physical and psychological dependence. This has important implications. It means that any criticism of the notion of addiction can be circumvented merely by referring to a different definition. Its vagueness and plurality make addiction a non-falsifiable concept. It is uncertain whether such concepts serve a useful function. The present analysis tries to avoid these problems by dealing with issues that are common to many, but never all, current definitions.

In a medico-legal context where the use of the term addiction has major implications for treatment, social policy, and litigation, one would expect a degree of definitional precision at least comparable to that of other major diagnostic categories. This sort of precision, or even a rough approximation thereof, is not available.

Addiction is commonly used to describe drug problems. There can be little objection to such loose everyday use of addiction. The difficulties arise when addiction is used to *explain* drug problems. There

is a persistent tendency to confuse description with explanation. There are substantial difficulties even when addiction is used in a descriptive sense. However, there are still greater difficulties when addiction is used to explain persistent drug use.

Hundreds of definitions of addiction have been published, but there is no agreement as to which, if any, should be used (Warburton, 1985). Apart from that of the Surgeon General, two other definitions have become *de facto* standards: they are that of the American Psychiatric Association (DSM-III-R) and World Health Organization. They and others will be considered below with special reference to the notion of nicotine addiction.

The Surgeon General's 1988 Report on Smoking and Health is easily the most influential document in this area. Because its definition occupies such a prominent place in addiction, it will be considered in some detail.

The central element among all forms of drug addiction is that the user's behavior is largely controlled by a psychoactive substance (i.e., a substance that produces transient alterations in mood that are primarily mediated by effects in the brain). There is often compulsive use of the drug despite damage to the individual or to society, and drug-seeking behavior can take precedence over other important priorities. The drug is "reinforcing"--that is, the pharmacologic activity of the drug is sufficiently rewarding to maintain self-administration. "Tolerance" is another aspect of drug addiction whereby a given dose of a drug produces less effect or increasing doses are required to achieve a specified intensity of response. Physical dependence on the drug can also occur, and is characterized by a withdrawal syndrome that usually accompanies drug abstinence. After cessation of drug use, there is a strong tendency to relapse. (United States Department of Health and Human Services, 1988, p. 7)

The Surgeon General's definition states that "the user's behavior is largely controlled by a psychoactive substance" (United States Department of Health and Human Services, 1988, p. 7). Whereas nicotine certainly affects behavior, it is questionable whether it can properly be said to control behavior. It has yet to be demonstrated that nicotine can exert more control over behavior than that exerted by any of scores of innocuous substances and events. Moreover, smoking is almost always done along with something else. The fact that smoking enhances a broad range of abilities (Pritchard & Robinson, 1994) suggests that the user's behavior is *not* controlled by the substance. In this context the behavioral consequences of nicotine are little different from those of eating a carrot.

Although the Surgeon General stresses that an addiction "takes precedence over other important priorities" (United States Department of Health and Human Services, 1988, p. 7), this rarely applies to smoking. The overwhelming majority of smokers know when they can and cannot smoke, and they usually find increasingly severe restrictions only a minor nuisance. Certain religions prohibit smoking on the Sabbath, and even the heaviest smokers report no difficulty in observing this rule (Shiffman, 1991). It is difficult to imagine a molecular dysfunction of the brain that respects the Sabbath.

The Surgeon General stresses that addictive substances are reinforcing (rewarding). We will see below that, at best, nicotine may be slightly more rewarding than saline. Even under the most carefully contrived circumstances, nicotine is probably no more rewarding than a flash of light or a brief sound. Such feeble reward does not suggest abuse potential.

Sugar can exert far more powerful and reliable effects over the behavior of both laboratory animals and humans than nicotine (Allsop & Miller, 1996; Bock, Kanarek, & Aprille, 1995; Davis, 1995; Gibney,

Sigman-Grant, Stanton, Jr., & Keast, 1995; Gold, 1995; Lindroos, Lissner, & Sjöström, 1996; McDonald, 1995). Moreover, much as is the case with nicotine, sugar has been associated with ill health (DiBattista & Shepherd, 1993; Furth & Harding, 1989; Wu, Yu, & Mack, 1997). Similar considerations apply to salt (Feldman, Logan, & Schmidt, 1996; Goldbloom, 1997; Kochar, 1992). The ability to control behavior and to produce adverse effects on health are certainly not adequate evidence that anything is addictive. Poorly-specified, overinclusive definitions subsume so many things that the entire issue becomes trivialized (Jaffe, 1990a).

Next the Surgeon General's definition refers to the substance use continuing: "...despite damage to the individual or to society" (United States Department of Health and Human Services, 1988, p. 7). However, smoking produces no damage in many people and most smokers respond to danger signs by stopping (Schachter, 1990). Few people with clear signs of smoking-related illness persist in smoking; they are not representative of smokers in general (Taylor, 1984).

In 1969 the World Health Organization discarded the term addiction and replaced it with dependence defined as:

A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. (World Health Organization, 1969, p. 4)

This definition is instructive for a number of reasons. First, it refers to a state that is psychic and sometimes also physical. Given that all states are probably both psychological and physical, this part of the definition excludes nothing and is thus uninformative.

Next the definition mentions the interaction between a living organism and a drug. Thus dependence concerns drugs. Then the definition refers to behavioral and other responses; this excludes nothing. Even the term 'compulsion' requires further specification since it may mean anything from a minor inclination to an overwhelming desire. The undefined compulsion to take the drug may either be on a continuous or periodic basis, which once again excludes nothing.

Next comes reference to the drug being taken out of the desire to experience its psychic effects. This appears to refer to drug effects on behavior, mood, or sensation. Under certain circumstances, nearly every substance taken by man is psychoactive. Merely being detectable could mean psychoactive (Goudie, 1991). This is another part of the definition that is so over-inclusive as to be meaningless.

Lastly, the definition specifies that tolerance may or may not be present. This widely used definition is an amalgam of ill-specified and over-inclusive catch phrases. It fails to meet the most minimal standards of a definition.

The vagaries in official views of nicotine addiction are reflected in the attitudes of the World Health Organization (WHO). WHO did not consider tobacco to be dependence producing until 1974 (WHO, 1974). Even in 1978 they still listed tobacco dependence separately because they said that tobacco was not psychotoxic (WHO, 1978). The American Psychiatric Association didn't recognize smoking as an addiction until 1980 in the DSM-III (APA, 1980).

The essential definitional inadequacies of addiction are sometimes addressed by referring to secondary

constructs such as craving, habit, psychological dependence, physical dependence, etc.(Goudie, 1991; Linsen, Zitman, & Breteler, 1995; Peele, 1977; Warburton, 1990a, 1990b, 1994a). However, rather than clarify the definition, these poorly-defined constructs merely obfuscate it (Nestler, Hope, & Widnell, 1993). Thus the current situation is based on fundamentally inadequate definitions, the problems of which are compounded by making reference to secondary explanatory constructs that are frequently even more poorly specified (Linsen, Zitman, & Breteler, 1995).

Some of the problems in this area reflect the intrusion of extra-scientific agenda: "...at least in the United States, definitions of addiction have come to be based more on legislative fiat and judicial rulings than on pharmacologic or clinical evidence" (Newman, 1983, p. 1097). In the 1964 report on smoking and health, the Surgeon General stated unequivocally that nicotine was *not* addictive (Ruxton & Kirk, 1997). In 1988 he reversed this view (US Department of Health and Human Services, 1988). There were no scientific or clinical breakthroughs in this interval, but there was a great deal of legal and political activity (Jones, 1992; Peele, 1992; Seltzer, 1997; Taylor, 1984; Vallin, 1984; Warburton, 1994b).

Any workable definition of addiction must differentiate between the use of innocuous substances and those that present a real danger. At the moment, none even approaches this most basic criterion. What use are definitions that cannot differentiate crack smoking from coffee drinking, glue sniffing from jogging, heroin injection from eating carrots, and snorting cocaine from drinking colas? (Hilts, 1994).

Existing definitions of addiction and related concepts do not appear to be valid scientific or medical concepts. They serve an important function in that they bring the use of certain substances within the province of the medical and legal professions (Chiauzzi & Liljegren, 1993; Coleman, 1976; Peele, 1977, 1986, 1987, 1990a).

No other diagnostic category suffers from anything like the definitional uncertainty that characterizes addiction (Goudie, 1991; Peele, 1977; Warburton, 1985). The fact that the combined efforts of thousands of scientists and legislators for fifty-odd years have not produced a single rigorous definition suggests that they may be trying to define an undefinable.

Animal Models of Addiction

Advocates of animal experimentation maintain that the essential features of human drug taking may be represented in other species (Hogg, 1996; Klopfer, 1996; Willner, 1991a). By allowing precise control of variables that inevitably remain uncontrolled in human experimentation, animal experiments offer important advantages (Mogensen, 1994). On the other hand, this very control complicates extrapolation across species. Human drug taking occurs in environments that are very different from those of laboratories.

Critics also point out that human drug taking is subject to many influences that can not be investigated in laboratory animals (Goudie, 1991; Slotkin, 1983; Willner, 1991b). It is difficult to imagine an unemployed, guilt-ridden rat, or a monkey suffering from low self-esteem. Peer pressure, which is so important in human drug use, has no parallel in lab species. It is questionable whether animals could correctly be said to 'abuse' drugs (Goudie). An animal that was chronically intoxicated would not lose its job, be evicted, shunned by its peers, or be jailed.

Most laboratory experiments measuring the rewarding properties of drugs use operant technology (Stolerman, 1993). The animal is placed in a small box inside a sound attenuated chamber. The bland uniformity of laboratory conditions is very different from the complex and changing environments in

which humans take drugs (Iwamoto & Martin, 1988; Richelle, 1989; Stephens, 1986; Woolverton, 1992). The uniformity and solitary confinement to which laboratory species are subject while taking drugs are stressful (Deroche, Piazza, Le Moal, & Simon, 1994; Kim & Kirkpatrick, 1996; Phillips, Howes, Whitelaw, Robbins, & Everitt, 1994; Phillips et al., 1994). Social isolation and stress undoubtedly play a role in human drug use, but in rodent models these factors appear to be of much greater importance. Since nicotine alleviates stress (Onaivi et al., 1994; Parrott, 1995; Pomerleau, 1986; Pomerleau & Pomerleau, 1991), any effects on pleasure (Lovaas, Newsom, & Hickman, 1987; Shoaib & Shippenberg, 1996) are confounded with stress reduction.

Experimental conditions used with primates are also very different from human drug-taking conditions. Primates are strapped into a chair and allowed just enough freedom of movement to press a lever. Laboratory paradigms reduce the animal's choice to taking the drug or doing virtually nothing. This is very different from human drug taking in which the subject typically has many behavioral options.

...animal drug self-administration requires a specific experimental environment and can be "turned off" by such minor modifications as increasing the amount of bar pressing required to obtain the drug. In other circumstances, animals can hardly be forced to take a drug.... Falk similarly noted animals that consume drugs and alcohol excessively when under extremely uncomfortable experimental conditions cease to do so as soon as normal laboratory conditions are reinstated. Findings like these led Dole (1980) to note: "Most animals cannot be made into addicts." In response to drugs reported regularly to addict human beings, "animals generally avoid such drugs when they are given a choice." (Peele, 1990a, p. 213)

Alexander's classic "Rat Park" experiments illustrate the difficulties in getting rats 'hooked' even after long periods of forced drug administration:

No matter how much we induced, seduced, or tempted them, the Rat Park rats resisted drinking the narcotic solution. The caged rats drank plenty, however, ranging up to sixteen times as much as the Rat Park residents in one experimental phase, and measuring ten times as much in some other phases. The females, curiously, drank more morphine in both environments, but the Rat Park rats always drank far less than the caged rats. (Alexander, Coombs, & Hadaway, 1980, p. 35)

Lab animals rarely, if ever, show any behavior that could reasonably be called addictive. When given no choice, they may self-administer drugs. However, when given alternative responses such as occur when they are housed with other animals, drug use is very infrequent (Dole, 1980). Indifference to drugs is also seen after long periods of forced exposure to morphine and alcohol (Gentry & Dole, 1987). Under certain conditions, animals may vigorously self-administer drugs, but they do not have any trouble stopping.

Self-administration may indicate reinforcement, and drugs such as heroin and cocaine are reinforcing. However, simply being reinforcing is not equivalent to being addictive. Animals vigorously self-administer sucrose, air, and many other innocuous substances. Vigorous self-administration may be a necessary condition for substance abuse, but it is not a sufficient condition.

Nicotine as a Psychoactive Substance

Nicotine meets some of the criteria for being psychoactive, although even here there is a good deal of definitional uncertainty. Altered transmission in nicotinic systems produces a wide range of effects on autonomic, endocrine, and neural processes (Ashton & Stepney, 1982; Carstens, Saxe, & Ralph, 1995; Grenhoff & Svensson, 1989; Gribkoff, Christian, Robinson, Deadwyler, & Dudek, 1988; Houlihan,

Pritchard, Kriebel, Robinson, & Duke, 1996; Murray, 1991). Humans and animals can usually tell when they have been given nicotine (Chandler & Stolerman, 1997; Mariathasan, Stolerman, & White, 1997; Mariathasan, White, & Stolerman, 1996; Perkins, D'Amico et al., 1996; Stolerman & Jarvis, 1995; Terry et al., 1996). However, being psychoactive is a necessary, but not sufficient, condition for abuse potential. A large number of psychoactive substances have no abuse potential.

Psychoactive is frequently used to mean mood altering, but the National Institute on Drug Abuse (NIDA) has given it a more specific meaning. Their definition refers to "...a distortion of the perception of time, space, and the location of objects within space...a dose-related reduction in physical coordination or psychomotor functioning" (Robinson & Pritchard, 1992, p. 399). This is very similar to definitions of intoxication. Nicotine does *not* produce anything like intoxication. Indeed, nicotine facilitates many cognitive and motor functions (Danion et al., 1997; Levin, Briggs, Christopher, & Rose, 1992; Rusted, Graupner, & Warburton, 1995; Rusted & Warburton, 1995; Warburton 1994c, 1994d; Warburton & Arnall, 1994). According to NIDA criteria, nicotine is not psychoactive.

Evaluating the role of nicotine in smoking is complicated by the fact that tobacco contains a number of other alkaloids (Benowitz, Porchet, & Jacob III, 1990). Nicotine, anabasine, myosmine, nicotyrine, and anatabine typically account for around 10% of the alkaloid content of tobacco (Dwoskin et al., 1995; Hoffmann, Adams, Piade, & Hecht, 1980). However, in some tobaccos these alkaloids may outweigh nicotine (Benowitz et al., 1990). Little is known about the psychopharmacology of these other alkaloids, but they appear to be quite potent (Benowitz et al., 1990). How they interact with each other and with nicotine is largely unknown. Thus nicotine self-administration is a poor model of even the alkaloid aspects of smoking. It is possible that some of these deficiencies may be rectified by using alkaloid mixtures that more closely approximate those encountered in tobacco.

Dose equivalence

The nicotine dose delivered by a typical cigarette is about 1.0 mg (Ashton & Stepney, 1982; Benowitz et al., 1990). In a 75 kg human, a cigarette yields a nicotine dosage of 13 µg/kg. If a cigarette is smoked in 20 puffs, the nicotine dose is .70 µg/kg/puff. Primate self-administration studies generally use 10-100 µg/kg/infusion (Wakasa, Takada, & Yanagita, 1995). Thus, the primate dose is 15-150 times higher than humans typically self-administer while smoking.

Even very heavy smokers self-administer nicotine nasal spray at a rate of only 200 µg/kg/day (Tonnesen, Mikkelsen, Norregaard, & Jorgensen, 1996). Humans can reliably detect nicotine at doses of 2 µg/kg delivered by nasal spray (Perkins, DiMarco, Grobe, Scierka, 1994). As little as 40 µg/kg of intravenous nicotine produces aversive effects in humans (Henningfield, Miyasato, & Jasinski, 1983). In regular smokers of 1.0 mg nicotine cigarettes, a single 2.4 mg nicotine cigarette often produces signs of nausea, sickness, and unpleasantness (Gilbert, Meliska, Williams, & Jensen, 1992).

The nicotine doses commonly used in animal experiments are in the range of those producing nausea and vomiting in humans and other species (Matsushima, Prevo, & Gorsline, 1995; Smith et al., 1996). Although there are few data on nicotine lethality, one report suggests that a bolus of less than 1 mg/kg is fatal in humans (Eysenck, 1965). Another suggests that an intravenous injection of the nicotine from one small cigar would be fatal (Royal College of Physicians of London, 1977).

The most common nicotine dose used in rodent self-administration studies is 30 µg/kg (Chiamulera, Borgo, Falchetto, Valerio, & Tessari, 1996; Corrigan & Coen, 1991a), which is over 40 times higher than typical human self-dosage. Studies in which nicotine is given as a pre-treatment use even higher doses. In

one such study, rats were given 400 µg/kg, which is over 500 times higher than humans self-administer in a single puff and more than twice as much as even very heavy smokers self-administer nasally over the course of an entire day (Tonnesen, Mikkelsen, Norregaard, & Jorgensen, 1996).

Typical experiments with laboratory species use nicotine doses that are equivalent to those achieved if a human consumed several cigarettes in a single puff. Humans find even much lower doses of nicotine aversive. Foulds et al. have shown that less than 10 µg/kg of intravenous nicotine causes dizziness, mood deterioration, and pain even in regular smokers. The nicotine pretreatment studies administer the equivalent of a full pack of cigarettes in a single dose. An investigation of receptor kinetics used 12 mg/kg/day (Kirch, Taylor, Creese, Xu, & Wyatt, 1992). This is the rough human equivalent of smoking 1,000 cigarettes.

It is unlikely that any human would ever self-administer nicotine doses even remotely approaching the lowest doses used in laboratory experimentation (Ashton & Stepney, 1982). The fact that laboratory species can withstand doses of nicotine that would be dangerous or lethal in humans suggests a major species difference. Because the metabolism of nicotine in the rat is quite different from that in humans, rabbits and hamsters may be more suitable subjects (George, 1993).

The issue of dose is particularly critical in considering the reinforcing effects of nicotine (see below). At high doses, nicotine produces marked effects on monoaminergic transmission (Vizi & Lendvai, 1999). Since dopamine, serotonin, and norepinephrine all have important roles in reinforcement (Berke & Hyman, 2000; Curtin et al., 1997; Di Chiara, 2000), high doses of nicotine could produce neurochemical effects quite unrelated to those of the low doses produced by smoking tobacco. The high, sometimes astronomically so, nicotine doses used in laboratory research with infra-human species confound behavioral and neurochemical investigations.

Nicotine, reinforcement, and addiction

The Surgeon General and other authorities emphasize the importance of reinforcement in the development of addiction (Colle & Wise, 1987; US Department of Health and Human Services, 1988). Few would disagree with the notion that a substance is unlikely to be abused if it is not liked. Although humans can be asked whether they like various substances, this issue can only be approached indirectly in laboratory species (De Wit & Griffiths, 1991). There are major unresolved problems in inferring complex psychological processes, such as liking from simple behaviors such as lever pressing (Goudie, 1991).

If laboratory species will voluntarily take a drug, it is assumed that humans will too. Laboratory species and humans vigorously self-administer heroin (Hand, Stinus, & Le Moal, 1989), morphine (Di Chiara, Acquas, & Carboni, 1992), cocaine (White, 1996; Woolverton, 1992), and amphetamine (Peltier, Li, Lytle, Taylor, & Emmett-Oglesby, 1996). Heroin, morphine, cocaine, and amphetamine sustain high rates of self-administration and are enjoyed and abused by humans. Moreover, the experimental literature is consistent for these drugs. Apart from sustaining vigorous self-administration, the self-administration is acquired quickly and easily. Failures to self-administer any of these drugs are rare (Iwamoto & Martin, 1988). Such data are consistent with abuse potential.

However, many drugs self-administered by laboratory species have no abuse potential in humans. These exceptions include the anti-hypertensive clonidine (Asin & Wirtshafter, 1985; Weerts & Griffiths, 1999), the appetite suppressant phentermine (Papasava, Singer, & Papasava, 1985a; Papasava, Singer, & Papasava, 1985b), the anti-schizophrenic drug chlorpromazine (Hoffmeister & Goldberg, 1973), and the

anti-depressants nomifensine and bupropion (Tella, Ladenheim, & Cadet, 1997). Iwamoto and Martin (Iwamoto and Martin 1988) add to this list: ketocyclazocine, ethylketocyclazocine, apomorphine, piribedil, procaine, N-allylnormetazocine, metazocine, and phenylethanolamine.

Conversely, laboratory species often do not self-administer drugs that humans do. These exceptions include tranquilizers (Lee, Flegel, Greden, & Cameron, 1988), hallucinogens (Stolerman, 1993), and cannabis (Frances & Franklin, 1996). Whereas humans find both tranquilizers and cannabis pleasant, rats are generally indifferent to them (McGregor, Issakidis, & Prior, 1996). Humans find alcohol, barbiturates and benzodiazepines reinforcing, but these drugs generally support only weak self-administration in laboratory species and failures to show reinforcement with these drugs are common (Ator & Griffiths, 1987; Dominguez, Bocco, Chotro, Spear, & Molina, 1993; Keane & Leonard, 1989; Meisch & Stewart, 1994).

The self-administration of nicotine is surrounded by uncertainty and controversy. This is reflected in Jaffe's assessment: "It has not been possible to develop reliable animal models of self-administration of tobacco products..." (Jarvik, 1977, p. 122). There are reports of failures to establish nicotine self-administration in spite of intensive efforts (Ator & Griffiths, 1983; Goudie, 1991). Although no infra-human species smokes, smoking can sometimes be established in primates. However, in marked contrast to humans, smoking in infra-human primates can only be established by coercive procedures (Ando, Hironaka, & Yanagita, 1986). Moreover, once established, smoking in primates does not produce any evidence of a habit; they stop at the first opportunity (Swedberg, Henningfield, & Goldberg, 1990; Wood, 1990).

Even when smoking is established in laboratory primates, it appears to be very different from that seen in humans. Primates do not inhale tobacco smoke. Rucker trained monkeys to puff cigarettes using water as a reinforcer (Wood, 1990). However, he details exhaustive and unsuccessful attempts to get the monkeys to inhale. Additionally, when the water reinforcement was discontinued, the monkeys immediately stopped puffing. Smoking does not appear to be reinforcing for laboratory primates.

Baboons can be coerced into smoking by making water contingent on their puffing (McGill, Rogers, Wilbur, & Johnson, 1978; Roehrs, Rogers, & Johanson Jr., 1981; Rogers et al., 1980; Rogers et al., 1988; Rogers, McCullough, & Caton, 1981; Rogers, Wilbur, Bass, & Johnson, 1985; Sepkovic et al., 1988). Unfortunately, none of these experiments reported whether the baboons would continue smoking when it was no longer required to obtain water. Others have also coerced laboratory primates into smoking (Ando, 1975; Ando, Hironaka, & Yanagita, 1986; Ando & Yanagita, 1981; Yanagita, Ando, Kato, & Takada, 1983). In the latter reports, even after the most intensive training efforts, the vast majority of the monkeys would not smoke. Given the coercive nature of the training and the amount of aversive stimulation (electric shock) given in these experiments, it is questionable whether even the few exceptional cases should be viewed as representative of human smoking.

The establishment of nicotine self-administration in laboratory species is time consuming and unreliable (Goldberg & Henningfield, 1988; Henningfield & Goldberg, 1983a; Naruse, Asami, Ikeda, & Ohmura, 1986; Swedberg et al., 1990). Moreover, once established, the rate of nicotine self-administration is very low. For example, Singer and Wallace (1984) show maximum nicotine self-administration rates that are scarcely greater than those supported by saline. This is far from being compulsive drug use. Animals will quickly learn to press a lever thousands of times per hour to get cocaine (Iwamoto & Martin, 1988; Ward et al., 1996). With nicotine, the highest self-administration rates ever reported in rats are around 25 per

hour (Corrigall & Coen, 1989).

Corrigall is one of the few researchers reporting consistent nicotine self-administration in rats (Corrigall, 1991; Corrigall & Coen, 1989, 1991a, 1991b, 1994a; Corrigall, Coen, & Adamson, 1994; Corrigall, Franklin, Coen, & Clarke, 1992; Rose & Corrigall, 1997). The credibility of these studies is increased by the fact that the rats were not food deprived nor were they previously trained for other drugs. Moreover, Corrigall's rats had access to an inactive lever that provided an index of response specificity. In addition, Corrigall's rats were trained to respond on a fixed interval of five seconds, and others have replicated his basic findings (Donny, Caggiula, Knopf, & Brown, 1995; Tessari, Valerio, Chiamulera, & Beardsley, 1995).

The Corrigall et al. findings are the best indicators that nicotine may be reinforcing in rats. Whether they are adequate demonstrations of reinforcement is open to question, but in any case, they do not indicate abuse potential. First, whereas the authors use the term robust self-administration, the highest response rate obtained in any of these experiments is about 25/hour. This sort of performance is near the very lowest rates of responding reported for any reinforcer. Woolverton (1992) has shown that monkeys respond at rates greater than 20 per hour for saline.

There is a more serious deficiency in the Corrigall and related papers. None appears to have used saline self-injection as a control for nonspecific injection effects. The data from Corrigall and Coen (1989) replotted by Stolerman and Shoaib (1991) show a flat dose-response curve that falls off only at a very high dose of nicotine (60 µg/kg). Since the lowest dose (3.0 µg/kg) is one-tenth of the most commonly used dose in this work, it could well be, in effect, a zero dose. If this is the case, then the responding at the two higher doses represents nothing more than operant rate of intravenous injections. This issue cannot be resolved until appropriate experiments are conducted. Until then Corrigall et al. self-administration studies may only be considered to be suggestive of weak reinforcement, nothing more.

Moreover, the few reports of self-administration of nicotine in laboratory species use intravenous administration. This is very different from the inhalation route by which humans normally take nicotine. Humans have been reported to find intravenous nicotine rewarding (Henningfield & Goldberg, 1983b), but nicotine injections have also been shown to be aversive (Goldberg & Spealman, 1982; Jarvik, 1977). Monkeys will work to *postpone* nicotine injections (Spealman, 1983). The fundamental uncertainties in this area are reflected in Jaffe's statement: "We don't even know for sure what the principal reinforcing ingredient in tobacco is" (Jarvik, 1977, p. 122).

There are two notable exceptions to the normally sluggish performance seen in nicotine self-administration experiments. Monkeys pressed a lever for a brief visual stimulus occasionally accompanied by an intravenous injection of nicotine (Goldberg, Spealman, & Goldberg, 1981). This second-order schedule produced lever-press rates much higher than anyone has ever reported for nicotine. However, there are a number of points that temper the usefulness of these data. First, three of the four monkeys had been previously trained on a similar schedule for cocaine. Additionally, in the absence of the signal, the monkeys performed as vigorously when the drug was no longer available. This suggests an extremely strange phenomenon. The peculiarity of these findings is further indicated by the fact that they have never been replicated. A single, well-controlled and replicable instance of vigorous nicotine self-administration would greatly strengthen the reinforcement thesis, yet no such instance exists.

Monkeys are capable of extraordinarily vigorous operant behavior. However, this vigor can also lead to interpretational difficulties. Monkeys may respond at extremely high rates for almost anything. They may make hundreds of thousands of responses to self-administer painful electric shocks (McKearney, 1968). This paradoxical behavior illustrates the problems in interpreting operant behavior. To infer reinforcement processes, let alone hedonic experience or addiction, from operant behavior requires numerous and tenuous assumptions.

Risner and Goldberg (1983) have reported mean breaking points of 390 responses for nicotine in beagles. This performance is vastly more vigorous than any seen in rats where 5 appears to be the highest breaking point rate ever achieved. As with his primate work (Goldberg, Spealman, & Goldberg, 1981), the finding with beagles has not been replicated. A common difficulty with both of the Goldberg studies is that the animals were previously trained to self-administer cocaine. Thus it is unclear to what extent the nicotine data merely represent an after-effect of the cocaine experience.

The fragility of nicotine self-administration is illustrated by large strain differences (Shoaib, Schindler, & Goldberg, 1997). Of four strains of rats, only two acquired nicotine self-administration, and even then it was weak and unreliable. Sprague-Dawley rats pretreated with either saline or nicotine showed some intravenous self-administration of nicotine. However, Long-Evans rats acquired the self-administration only when pretreated with saline. It is puzzling why nicotine pretreatment would inhibit the establishment of self-administration in one strain and facilitate it in another.

Fisher and Lewis inbred strains failed to acquire nicotine self-administration under any conditions (Shoaib et al., 1997). To establish *any* self-administration of nicotine requires the right strain of animal, the right pretreatment, and optimizing numerous other parameters as well (Wakasa et al., 1995). The crucial combination of so many and such diverse parameters indicate that this is not a robust phenomenon. It is not one that suggests abuse potential.

There are large contrasts in the acquisition of nicotine self-administration as compared to reference drugs of abuse. When nicotine injections only require making a few responses, monkeys take from *two to nine months of daily training* before they respond at rates higher than for saline (Swedberg et al., 1990). In contrast, they quickly learn to make thousands of responses for a single injection of cocaine (Ambrosio et al., 1996; Foltin & Fischman, 1994; Tella, Ladenheim, Andrews, Goldberg, & Cadet, 1996).

Animals self-administer aspirin (Hoffmeister & Wuttke, 1973) and caffeine (Atkinson & Enslin, 1976; Deneau, Yangita, & Seevers, 1969; Sekita et al., 1992). As with nicotine, aspirin and caffeine self-administration is not very vigorous and sometimes it may not occur at all (Heishman & Henningfield, 1992). Since adverse effects on health have been associated with both aspirin and caffeine (Bednar & Gross, 1999; Kiyohara et al., 1999) as with nicotine, their use could be seen as meeting the principle criteria for addiction.

Rats cannot be trained to smoke, but they can be trained to take nicotine orally. If nicotine is reinforcing, it should enhance the reinforcing value of the solution in which it is presented. However, nicotine does *not* enhance the reinforcing value of any solution (Robinson, Marks, & Collins, 1996; Smith & Roberts, 1995). To the contrary, as the nicotine concentration increases, the rats drink progressively less of the solutions.

As models of human addiction, laboratory self-administration experiments lack face validity (Goudie, 1991). In marked contrast to humans, laboratory species do not appear to organize their lives around any

drugs (Dole, 1980). Quite simply, there is no evidence that laboratory animals ever get "hooked." This is particularly true of nicotine where there is not even the slightest suggestion of compulsive use in laboratory species. Since getting *any* voluntary use of nicotine is difficult, it seems unlikely that compulsive use will ever be demonstrated.

The self-administration model also lacks predictive validity (Goudie, 1991). Many drugs that humans abuse are not self-administered in laboratory species and vice versa. These false positives and negatives greatly reduce the usefulness of information derived from such paradigms. The fact that there is some concordance for certain drugs suggests that such experimentation may elucidate the human use of these drugs. However, nicotine is not one of the drugs for which there is a reasonable degree of concordance.

Sensory-contingent Reinforcement

Rats can be trained to press a lever simply to get a brief flash of light (Glow & Russell, 1973; Glow & Winefield, 1979, 1982; Winefield & Glow, 1980). This behavior is at least as vigorous and reliable as nicotine self-administration. In a uniform environment with few options, rats will do a little of almost anything (Lovaas et al., 1987). Rats will lick at a drinking tube through which a stream of air is passing or even just a chilled drinking tube (Mendelson & Chillag, 1970a, 1970b; Mendelson, Zec, & Chillag 1971, 1972). These strange behaviors are much more vigorous than nicotine self-administration, yet few would be willing to attribute abuse potential to air or cold metal. Under certain circumstances, unusual, even compulsive, behavior can be produced in laboratory species. However, there are no remotely comparable human behaviors. This lack of face validity means that it is perilous to use these laboratory anomalies as models of any human behavior.

Place Preference

In drug self-administration experiments, the animals are tested while under the influence of the drug. This means that drug side-effects can be confused with changes in the motivation to take the drug. One way around the performance problem is to test the animals when they are not under the influence of the drug. For example, if a rat is given heroin or cocaine in a distinctive environment, they come to prefer the environment in which the drug was given (Perks & Clifton, 1997). They appear to remember the positive experience, and the preference may last for many weeks. The place preference procedure is minimally affected by behavioral incapacitation since the animals are tested in a non-drugged state.

Place preference experimentation provides only weak and equivocal support for nicotine being rewarding. The tone for this work was set some time ago. "Although nicotine has been reported to produce conditioned place preference, the present results suggest that it is not a robust phenomenon" (Clarke & Fibiger, 1987, p. 84). Some have failed to get a place preference with nicotine (Clarke & Fibiger, 1987; Parker, 1992). Others have shown place aversion (Jorenby, Steinpreis, Sherman, & Baker, 1990). Still others have shown both preference and aversion in the same experiment (Calcagnetti & Schechter, 1994; Shoaib, Stolerman, & Kumar, 1994). Much like the self-administration experiments, these experiments show that if nicotine has any rewarding properties at all, they are both weak and unreliable. Such findings do not suggest abuse potential.

The state of the animal literature on the rewarding properties of nicotine has been summarised by Collins (1990): "Studies do not provide unequivocal evidence for nicotine producing reward either via euphoric actions or through reduction of pain, anxiety, or negative affect" (p. 20).

Conditioned Taste Aversion

Conditioned taste aversion is another technique for evaluating the motivational properties of drugs

(Andrews & Holtzman, 1987; Franklin & Robertson, 1992; Hunt & Atrens, 1992; Hunt, Atrens, & Jackson, 1994; Lin, Atrens, Christie, Jackson, & McGregor, 1993; Olds, 1994; Wise & Munn, 1993). If cocaine or amphetamine is administered at the time the animal is exposed to a novel flavor, on subsequent exposure to the flavor the rats show an aversion for it. It is paradoxical why the same experience can produce a place preference and a taste aversion (Grigson, 1997). Since clearly aversive substances such as lithium chloride also produce taste aversion (Bourne, Calton, Gustavson, & Schachtman, 1992; Turenne, Miles, Parker, & Siegel, 1996), the taste aversion model appears to have little face validity (Parker, 1991).

As with the other models of reinforcement, the data concerning nicotine and place preference are inconsistent. For example, some strains of mice show conditioned taste aversions, but others do not (Risinger & Brown, 1996). Another experiment showed that only extremely high doses of either amphetamine or nicotine produced conditioned taste aversions (Parker, 1991). These doses did not produce a place preference. Thus one model suggests reinforcement, but the other does not.

Reinforcement in Humans

There is one widely cited paper suggesting that nicotine is powerfully reinforcing for humans (Henningfield, Miyasato, & Jasinski, 1985). Humans reported that intravenous injections of nicotine felt similar to cocaine. The face appeal of these findings is reduced by methodological problems. First, all of the subjects were hospitalized with unspecified histories of substance abuse. Additionally, some of the subjects who reported that nicotine was like cocaine had never experienced cocaine (Clark, 1990). Additionally, some subjects thought nicotine was like cannabis, morphine, or Valium®. Such gross errors suggest that the subjects were fairly confused. Some subjects reported a "rush" from the nicotine injection. Considering that they were given the nicotine content of three cigarettes in one bolus, such an effect is not surprising. High doses of nicotine often produce dizziness (Perkins et al., 1994).

Another study in a similar group of patients reported that intravenous caffeine produced subjective effects similar to those of cocaine (Rush, Sullivan, & Griffiths, 1995). These subjects identified caffeine as cocaine more often than they identified cocaine as cocaine! The subjective reports of intravenous drug users are influenced by many processes with little relevance to human drug taking (Iwamoto & Martin, 1988).

Paid volunteers given 40 µg/kg of intravenous nicotine reported transient respiratory problems, tightness in the chest, and feeling faint (Henningfield, Miyasato, & Jasinski, 1983). Paradoxically, it was only this dose that produced reports of liking. On the other hand, one of the subjects said he would pay *not* to have another injection. These data do not suggest reinforcing effects of nicotine that are in any way comparable to those of drugs such as cocaine or heroin.

The above experiments and many others illustrate the difficulties with introspection (Altman et al., 1996; Chiauzzi & Liljgren, 1993; Fischman & Foltin, 1991; Henningfield, Cohen, & Heishman, 1991). If these experiments showed that the hedonic effects of nicotine were at all similar to drugs such as cocaine, the findings would still be difficult to interpret. However, the human experiments show such weak and inconsistent hedonic effects of nicotine that they do not merit extensive interpretational effort.

The fact that smokers generally prefer regular cigarettes to nicotine-free cigarettes suggests the importance of nicotine to smoking. However, nicotine-free cigarettes differ from regular cigarettes in numerous respects apart from nicotine content (Ashton & Stepney, 1982; Eysenck, 1965; Westman, Behm, & Rose, 1996). If nicotine is the basis of cigarette smoking, adding nicotine to nicotine-free

cigarettes should greatly increase their acceptability. Jaffe describes his experiments in this area: "The fact that lettuce cigarettes reinforced with nicotine were not accepted more than non-nicotine cigarettes has been a cause for concern and seriously undermined our support of the pure nicotine hypothesis" (Jarvik, 1977, p. 141).

In another study, smokers rated a nicotine-free cigarette as pleasant as their regular brand. The same subjects reported that a high nicotine cigarette was *less* pleasant (Gilbert et al., 1992). Although smokers find smoking pleasant, the pleasantness is a mild effect that bears no relationship to the powerful hedonic effects of drugs of abuse (Russell, 1989). The dissociation of nicotine from the reinforcing properties of smoking is further indicated by the fact that nicotine chewing gum produces mildly unpleasant effects and has little abuse potential (Henningfield & Keenan, 1993; Hughes et al., 1989; Nemeth-Coslett, Henningfield, O'Keeffe, & Griffiths, 1987).

In summary, the literature on nicotine reinforcement in humans is congruent with that from laboratory species. If nicotine is reinforcing, it is only weakly so. It is no more reinforcing than caffeine or many other innocuous substances. Nicotine reinforcement is not in any way comparable to the powerful and consistent effects produced by reference drugs such as cocaine and heroin. These findings provide no support for the notion that nicotine is sufficiently reinforcing to suggest abuse potential.

Interpreting Behavioral Persistence

Many find it difficult to quit smoking. This is reflected in high relapse rates of those in smoking cessation programs (Brigham, Henningfield, & Stitzer, 1990; Chassin, Presson, Rose, & Sherman, 1996; Fisher, Lichtenstein, Hairejoshu, Morgan, & Rehberg, 1993; Gibbons, Eggleston, & Benthin, 1997; Grunberg et al., 1995; Hymowitz & Eckholdt, 1996; Law & Tang, 1995; Schneider et al., 1996; Ter, Kleijnen, & Knipschild, 1990). The vast majority of successful quitters simply quit (Kozlowski & Schachter, 1975; Lennox & Taylor, 1994; Schachter, 1977, 1982, 1983, 1990; Schachter, Silverstein, & Perlick, 1977; Silverstein, Kozlowski, & Schachter, 1977). Moreover, many quit with little or no difficulty (Brauer, Hatsukami, Hanson, & Shiffman, 1996; Shiffman, 1989; Shiffman et al., 1995; Shiffman et al., 1994; Shiffman, Paty, Gnys, & Zettler-Segal, 1992). Strong resistance to change is not a general characteristic of smoking.

Whereas the public and professionals alike find addiction a convenient explanation for behavioral persistence, there are other explanations that are at least equally plausible (Ritzman, 1992; Warburton, 1994a, 1994c, 1994d, 1995). In any case, no explanation at all is always preferable to a bad explanation. The fact that humans engage in many behaviors in spite of numerous warnings of the attendant harms is not evidence of addictive processes. It is testimony to human frailty and the ineffectiveness of fear in controlling behavior.

Addiction and the Brain

Addiction is commonly portrayed as a brain disease (Anonymous, 1997; Balter, 1996; Brautbar, 1995; Dani & Heinemann, 1996; Leshner, 1996; Nash, 1997; Nutt, 1996; Rose, 1996). In spite of such claims, there is no brain pathology or even special brain state uniquely associated with the use of any drug in any species. Drugs of abuse change brain function (Di Chiara, 1995; Joseph, Young, & Gray, 1996; Peele, 1990c). However, similar changes are also produced by relatively innocuous substances and everyday events (Hernandez & Hoebel, 1988a, 1988b; Pfaus, Damsma, Wenkstern, & Fibiger, 1995; Wilson, Nomikos, Collu, & Fibiger, 1995; Yoshida, Yokoo, Mizoguchi, Kawahara, Tsuda, Nishikawa, & Tanaka, 1992; Young, Joseph, & Gray, 1992). Such changes cannot reasonably be said to represent the neural

substrate of addiction.

Some of nicotine's effects on dopamine resemble those of reference drugs, such as cocaine and amphetamines (Fung, Schmid, Anderson, & Lau, 1996; Koob, 1996; Levin, Kim, & Meray, 1996; Pich et al., 1997; Pontieri, Tanda, Orzi, & Di Chiara, 1996). These effects are consistent with abuse potential. However, there is also a great deal of evidence arguing against a major role for dopamine in nicotine's effects (Acquas, Carboni, Leone, & Di Chiara, 1989; Balfour, 1994; Corrigall & Coen, 1994b; Horger, Valadez, Wellman, & Schenk, 1994; Stolerman, 1991). These data will be discussed below.

Dopamine and the Nucleus Accumbens

Investigations of the neural basis of addiction have focused largely on the nucleus accumbens and the neurotransmitter, dopamine (Blum, Cull, Braverman, & Comings, 1996; Corrigall et al., 1994; Corrigall et al., 1992; Di Chiara et al., 1992; Koob & Weiss, 1992; Nisell, Nomikos, & Svensson, 1995; Robbins & Everitt, 1996; Self, McClenahan, Beitner-Johnson, Terwilliger, & Nestler, 1995; Self & Nestler, 1995; Volkow et al., 1997). This has led to what has become known as the dopamine hypothesis of reward (Salamone, Cousins, & Snyder, 1997). According to this view, the nucleus accumbens dopamine system is the final common denominator of diverse types of reinforcement (Koob, 1996; Koob & Bloom, 1988; Mitchell & Epstein, 1996; Wise, 1994, 1996a, 1996b, 1997; Wise & Leeb, 1993).

Amphetamine, cocaine, and morphine increase dopamine metabolism in the nucleus accumbens (Di Chiara & Imperato, 1988; Pontieri, Tanda, & Di Chiara, 1995). These drugs are frequently associated with problem use. Nicotine also increases dopamine metabolism in the nucleus accumbens (Benwell, Holtom, Moran, & Balfour, 1996; Mirza, Pei, Stolerman, & Zetterström, 1996; Pontieri et al., 1996), and this is used as evidence that nicotine is addictive (Pich et al., 1997). However, several considerations suggest that such a conclusion may not be warranted. Like nicotine, cannabis and synthetic cannabinoids also increase extracellular dopamine in the accumbens (Tanda, Pontieri, & Di Chiara, 1997). Saccharin also has similar effects (Mark, Blander, & Hoebel, 1991). The effects of cannabis, saccharin, and synthetic cannabinoids are further evidence of the broad range of stimuli that increase extracellular dopamine release. Mild tail pinches also increase extracellular dopamine in the shell of the accumbens (Brake, Noel, Boksa, & Gratton, 1997). Whatever increased extracellular dopamine in the accumbens may mean, and this is by no means clear (Di Chiara, 1995; Di Chiara, Tanda, & Carboni, 1996), it is not an indicator of addictive potential.

Additionally, the effect of these drugs on dopamine metabolism could simply be due to motor activation. All of these drugs stimulate motor activity, and the nucleus accumbens is an important part of the brain's motor control circuitry (Angulo & McEwen, 1994; Salamone, Cousins, & Snyder, 1997). Locomotor activity also increases dopamine metabolism (Sabol, Richards, & Freed, 1990). Further, the effect of nicotine on dopamine metabolism is extremely small--from one third to one sixth of that produced by reference drugs. Thus, in terms of its effects on dopamine metabolism in the nucleus accumbens, nicotine has quantitatively weak commonality with reference drugs. It is more similar to numerous other innocuous substances and events.

Dopamine release in the nucleus accumbens is not even unequivocally associated with positive reinforcement. Dopamine may be released by a neutral stimulus (Young, Joseph, & Gray, 1993) as well as a variety of aversive events including tail shock, foot shock, restraint, and release from restraint (Joseph, Young, & Gray, 1996). Gratton has recently reported similar effects of stress (Doherty & Gratton, 1996; Noel & Gratton, 1995). Thus enhanced dopamine release in the accumbens may mean

almost anything; it is not an unequivocal indicator of anything.

Additionally, the enhanced release of dopamine in the nucleus accumbens reported by Di Chiara and Imperato (1988) was produced by an extremely high dose of nicotine (600 µg/kg). The equivalent human dose would be about 50 cigarettes taken at once. Reid, Ho, and Berger (1996) also found increased dopamine release in the nucleus accumbens in response to 600 µg/kg but only in rats that had been conditioned to the testing environment. Nisell, Nomikos, Hertel, Panagis, and Svensson (1996) also obtained enhanced dopamine release in the accumbens with 500 µg/kg. Others have also found enhanced dopamine release in the accumbens at slightly lower nicotine doses (Benwell, Balfour, & Khadra, 1994; Mirza et al., 1996; Shoaib & Shippenberg, 1996).

All of the experiments described above used nicotine doses at least an order of magnitude greater than those used in animal self-administration experiments (typically 30 µg/kg) (Chiamulera et al., 1996; Corrigan & Coen, 1991a). Since self-administration of nicotine falls off at even 60 µg/kg (Stolerman & Shoaib, 1991), it appears that the nicotine doses used in the dopamine release work would be aversive. One hundred µg/kg of nicotine given intravenously produces whole body tremor even in rats given hexamethonium bromide to reduce peripheral effects (McNamara, Larson, Rapoport, & Soncrant, 1990).

There is only one study of dopamine metabolism that has used nicotine doses in the range of those self-administered by laboratory species (Pontieri et al., 1996). An intravenous bolus of nicotine (25 µg/kg) had no effect on glucose utilization. However, a higher dose (50 µg/kg) increased energy metabolism in the accumbens. These data stand in contrast to demonstrations that intraperitoneal, subcutaneous (London, Connolly, Szikszay, Wamsley, & Dam, 1988; McNamara et al., 1990) or continuous intravenous infusions (Grunwald, Schrock, & Kuschinsky, 1987) of nicotine have no effect on dopamine metabolism in the accumbens.

The tenuous relationship of dopamine release in the accumbens to behavioral processes is indicated by the effects of dopamine antagonists and neurotoxic lesions. Tone-shock pairings release dopamine in the accumbens, yet systemic or intra-accumbens administration of dopamine antagonists has no effect on the learning or retention of the association (Joseph, Young, & Gray, 1996). Moreover, low doses of systemically-administered dopamine antagonists may *enhance* reinforcement (Smith, Neill, & Costall, 1997). Selective neurotoxic lesions of the dopamine terminals in the accumbens before training also have no effect on the above association (Gray et al., 1995). It is premature to use dopamine release in the nucleus accumbens as a definitional characteristic of any aspect of drug use.

Compulsive Drug Use

Injury and death associated with the use of opiates and stimulants in humans are common (Benbow, Roberts, & Cairns, 1996; Darke & Zador, 1996; Logan, Weiss, & Harruff, 1996; Mash, 1997; Osterwalder, 1996). Being able to model this lethal aspect of drug use would be of great value. However, self-induced drug-associated deaths in laboratory species are rare. An exception is Bozarth and Wise's (Bozarth & Wise, 1985) report of a poor health and high mortality in rats given free access to intravenous cocaine and heroin.

Drug self-administration that leads to injury or death in laboratory species is commonly used to indicate that the drug in question has addictive potential (Dworkin, Mirkis, & Smith, 1995; Epling & Pierce, 1994; Koob, 1992, 1996). However, there are more parsimonious explanations for such maladaptive behavior. For example, food deprived rats given access to a running wheel may run and starve themselves to death (Beneke, Schulte, & Vander Tuig, 1995; Pierce & Epling, 1991; Rieg & Aravich,

1994). The anorexia and weight loss are similar to that reported by Bozarth and Wise (1985) during drug self-administration. Recent experiments have led to a fundamental reinterpretation of this behavior. If rats are given experience with the altered feeding schedule before they are given access to the running wheels, the excessive running and self-starvation do not occur (Boakes & Dwyer, 1997; Dwyer & Boakes, 1997). The self-destructive behavior merely reflects the rat's inability to adjust to altered conditions of feeding (Boakes & Dwyer; Dwyer & Boakes). In laboratory species, even behavior that appears to be sufficiently compulsive to lead to ill health and death requires cautious interpretation.

Tolerance

Although tolerance was long considered an important indicator of addiction, in 1969 WHO relegated it to a minor role. On the other hand, the Surgeon General still gives it a prominent place (US Department of Health and Human Services, 1988). It is peculiar to include tolerance as an indicator of addiction since tolerance is a common characteristic of responding to most forms of stimulation in almost all physiological systems (Atrens & Curthoys, 1982; Kalat, 1992).

As with nearly every other drug, tolerance has been shown to nicotine effects in laboratory species (Bullock, Barke, & Schneider, 1994; Damaj, Welch, & Martin, 1996; Domino & Lutz, 1973; Geng, Savage, Razanai-Boroujerdi, & Sopor, 1996; McAllister et al., 1994; Villanueva, James, & Rosecrans, 1989) and humans (Becona & Garcia, 1995; Henningfield & Keenan, 1993; Ochoa, 1994; Parrott, 1994; Perkins et al., 1994; Perkins et al., 1995). At the same time, it is noteworthy that these experiments show that tolerance occurs to some of nicotine's effects but not to others. Nicotine tolerance is a highly specific, not a general, phenomenon.

The major problem with tolerance as a criterion of addiction is the lack of any reasonable explanation of why it should indicate addiction. Tolerance occurs in diverse systems in response to nearly every substance encountered by every species. The mere fact that tolerance may be a conspicuous aspect of opiate use is not sufficient reason to elevate this ubiquitous phenomenon to the status of a symptom of addiction.

Withdrawal and Craving

In contrast to the dubious conceptual status of tolerance as an element in the definitions of addiction, there are reasonable grounds for including withdrawal. Withdrawal and associated craving are widely thought to be the main forces that drive relapse from drug abstinence (Henningfield, Gopalan, & Shiffman, 1998; Klein, 1998; Weaver, Jarvis, & Schnoll, 1999). However, there are major deficiencies in this approach. Even with opiates, the role of withdrawal in relapse remains in doubt (DuPont, 1998; Hughes, Higgins, & Bickel, 1994).

Many years of intensive investigation have failed to identify nicotine withdrawal effects that persist for more than a few weeks, at the very most (Hughes, 1992). In contrast, the tendency to relapse to smoking may persist for years (Henningfield et al., 1998; Patton et al., 1998; Razavi et al., 1999). The great differences in the temporal courses of withdrawal and relapse potential suggest that withdrawal cannot be a significant factor in relapse. Thus, withdrawal fails to account for the very behavior that it was invoked to explain (Satel, Kosten, Schuckit, & Fischman, 1993). A recent review stated: "It is concluded that the research to date does not appear to strongly implicate nicotine withdrawal in adversely affecting smoking cessation or maintenance of abstinence" (Patten & Martin, 1996, p. 190).

West, Russell, Jarvis, & Feyerabend (1984) investigated the effects in smokers of switching to an

ultra-low nicotine cigarette. They found an increase in hunger and decrease in heart rate but "...other common cigarette withdrawal symptoms, such as irritability, depression, and inability to concentrate, were not detected" (p. 120). Increased hunger and decreased heart rate are reliably associated with smoking cessation (Altman et al., 1996), but the other symptoms are not. The failure to find consistent psychological signs of abstinence is significant since it is this constellation of psychological dysfunction that is said to be the reason for relapse to smoking (Benowitz, 1996; Griffiths, 1996; Heishman et al., 1997; Kozlowski et al., 1989; Scholte & Breteler, 1997).

Craving is often invoked as a cause of relapse (Jaffe, 1990b). Craving has been characterized as an intense motivational state that arises as a consequence of withdrawal (Markou et al., 1993). However there is no workable definition of or procedure for measuring craving in any species (Altman et al., 1996; Tiffany, 1991). Until this deficiency is rectified, invoking craving merely further obfuscates an already confused area.

Human brain imaging studies have shown relatively long-duration changes in brain function of smokers, but the authors point out that it is unclear whether such changes are relevant to, let alone cause, withdrawal and/or craving (Kuhar & Pilotte, 1996). Changes in monoamine oxidase A activity in the rat brain following chronic high doses of nicotine have also been reported (Bhattacharya, Chakrabarti, Sandler, & Glover, 1995). However, apart from the fundamental problem of what such changes mean, it is not clear whether they occur to reasonable doses of nicotine and whether they last longer than 14 days. Indeed, given the monoaminergic effects of high nicotine doses (Sershen, Toth, Lajtha, & Vizi, 1995; Vizi & Lendvai, 1999), it is not even clear whether these may be considered true nicotine effects.

In spite of the widespread acceptance of withdrawal symptoms as an index of addiction (Benowitz, 1988; Koob, Sanna, & Bloom, 1998; Lyvers, 1998; West, 1984), this consensual faith does not appear to be justified. Striking, even dangerous withdrawal symptoms are also produced by antidepressants, antihypertensives, neuroleptics, and steroids (Haddad, 1999; Hughes et al., 1994). None of these diverse types of drugs has abuse potential, and humans tend to find them unpleasant. However, polydrug users may sometimes abuse almost any drug, including antidepressants (Kaminer, 1994).

The nicotine withdrawal literature is full of contradictions. For example, although anxiety is one of the commonest withdrawal symptoms, it is often not seen in animal models (Grasing, Wang, & Schlussman, 1996). Alternately, signs of anxiety are seen in some models and not in others and only under highly specific conditions (Balfour, 1994). Moreover, anxiolytic drugs are of little use in treating withdrawal in either animals or humans (Goudie & Leathley, 1995; Schneider et al., 1996). Even when nicotine withdrawal symptoms can be produced in laboratory species, they are very short lived. After seven days of continuous intravenous nicotine infusions, withdrawal signs in rats were not detectable after 16 hours (Malin et al., 1992).

Nicotine Replacement Therapy

The beneficial effects of nicotine replacement therapy on smoking cessation are often used in support of the nicotine addiction hypothesis. Nicotine replacement therapy may have significant effects (Hjalmarsen, Nilsson, Sjöström, & Wiklund, 1997; Law & Tang, 1995; Silagy, Mant, Fowler, & Lodge, 1994a, 1994b). However, these effects are modest and vary considerably. There have been numerous failures of nicotine replacement therapy (Jorenby et al., 1999; Patten & Martin, 1996; Schneider et al., 1996; Sonderskov, Olsen, Sabroe, Meillier, & Overvad, 1997). Almost any smoking cessation treatment is effective in the short term, but the effectiveness diminishes progressively at longer follow-up intervals

(Curry, Grothaus, McAfee, & Pabiniak, 1998; Jones, Nguyen, & Man, 1998; Razavi et al., 1999).

It is even possible that the effects observed in nicotine replacement therapy are not true pharmacological effects. The double-blind placebo trials use inactive agents to control for placebo effects. However, inactive agents are a poor placebo for an easily discriminable drug such as nicotine (Gilbert et al., 1992; Henningfield, Miyasato, & Jasinski, 1983; Perkins et al., 1994). There is evidence that the sensory experience provided by nicotine, apart from its pharmacological properties, may be important. Reduced craving in abstinent smokers has been produced by the vapor of black pepper (Rose & Behm, 1994) and citric acid (Westman, Behm, & Rose, 1995). By providing a facsimile of the oral and bronchial stimulation caused by tobacco smoke, the black pepper vapor and the fumes of citric acid functioned much like tobacco.

In any case, the success or lack thereof of nicotine replacement is orthogonal to the question of whether nicotine is addictive. There is no doubt that nicotine is involved in smoking, but whether its involvement is that of an addictive substance has yet to be demonstrated.

Conclusions

The notion of nicotine addiction suffers from numerous and major conceptual, definitional, and empirical inadequacies. Some reflect general problems with the concept of addiction, whereas others are specific to nicotine.

A recurring source of difficulty for the nicotine addiction hypothesis is the continuing lack of consensus concerning a definition of addiction. Hundreds of definitions have been offered, yet none withstands any scrutiny. Rigorous definitions of addiction clearly exclude nicotine, whereas those that reasonably include nicotine also include so many other substances and events that the notion of addiction becomes trivialized.

Lacking a reasonable definition of addiction, the putative addictiveness of drugs has become a matter of legislative fiat, judicial rulings, and committee edicts. Not surprisingly, which drugs are considered addictive varies markedly over time and in different places. Cannabis was long considered to be the scourge of our youth while tobacco was considered relatively harmless. Recently this position has been reversed. This is not science, but politics.

Self-administration studies in laboratory species are said to support the view that nicotine, much like heroin and cocaine, is powerfully reinforcing. However, nicotine self-administration doesn't remotely approach the vigor or reliability of that supported by drugs such as cocaine and heroin. The strongest reinforcing effects of nicotine in laboratory species are less than those of innocuous reinforcers such as light, sound, sugar, or salt.

Moreover, nicotine self-administration requires doses that are far higher than humans ever encounter. These effects may well represent monoaminergic effects of high nicotine doses. There are no reports of nicotine self-administration in laboratory species at doses even approaching those self-administered by humans. It is unjustified to use weak and inconsistent reinforcement effects obtained with high intravenous doses in laboratory species as evidence for human abuse potential.

Perhaps the most serious deficiency in using animal models to study human drug taking is that animals do not seem to get 'hooked' on any substance. This is particularly true of nicotine. It is difficult to show any rewarding effects of nicotine in laboratory species, let alone the powerful effects associated with drugs of abuse. It is possible that drug abuse is a uniquely human phenomenon.

Like the data from animal experimentation, the data on nicotine reinforcement in humans do not suggest that nicotine has abuse potential. There are no credible demonstrations in humans that nicotine is any more reinforcing than many other substances and events that have no abuse potential. The subjective effects of nicotine suggest a drug that is pleasant, nothing more. In this crucial respect, nicotine contrasts markedly with reference drugs such as cocaine and heroin that consistently produce strong feelings of euphoria.

There have been attempts to lend credibility to the notion of addiction by describing it as a brain disease. However, there is little evidence for such a view. There is no special brain state associated with nicotine use. Although nicotine has diverse effects on the brain, none has any significant potential to perpetuate nicotine use. Moreover, the neural effects of nicotine and other putatively addictive drugs are indistinguishable from those produced by many relatively harmless substances and everyday experiences.

Nicotine has effects on dopaminergic transmission that, in certain respects, resemble those of cocaine or heroin. However, almost anything that alters arousal alters dopaminergic transmission. Such neurochemical effects should not be interpreted as a correlate of addiction. The fact that some of the effects on dopamine transmission may be restricted to the shell of the nucleus accumbens is interesting, but irrelevant to whether nicotine or anything else is addictive.

The finding that dopamine may be involved in the effects of nicotine and reinforcement processes lends no support to the notion that nicotine is addictive. The dopamine hypothesis of reinforcement remains an intensely debated issue in which the theory, methodology, and empirical findings are all disputed. Claims to the contrary notwithstanding, none of the many variants of the dopamine theory has, as yet, any implications for human drug use. There is no justification for making the major leap from the poorly understood neural sequelae of reinforcement in laboratory species to the still more poorly defined and understood notion of addiction in humans.

The effects of nicotine, like those of virtually every other drug, psychoactive or not, show a degree of tolerance. It is questionable whether this ubiquitous phenomenon says anything about abuse potential. It certainly does not distinguish nicotine from many other innocuous substances.

Nicotine use may sometimes produce withdrawal effects. However, many drugs with no abuse potential produce withdrawal effects that are much more dramatic than those produced by nicotine. Conversely, many drugs with substantial abuse potential produce little in the way of withdrawal effects. Additionally, nicotine withdrawal effects last for no more than a few weeks, whereas relapse potential may last for years. The fact that withdrawal and relapse potential have such different temporal characteristics indicates that they cannot be causally related.

In summary, apart from numerous conceptual and definitional inadequacies, the notion that nicotine is an addictive substance lacks reasonable empirical support. There are so many and such grossly conflicting findings that adhering to the nicotine addiction thesis is only defensible on political, not scientific, grounds. More broadly, addiction may have some use as a description of certain types of behavior, but it fails badly as an explanation of such behaviors.

It is commonly assumed that questioning the addiction hypothesis is to condone and even advocate drug use. Such an assumption is incorrect. In order to develop effective treatments for drug problems, it is necessary to escape from the unproductive ideology that is currently dominant. Abandoning the concept of addiction is a step in this direction.

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